REMARKS/ARGUMENTS

Claims 384, 386, 387, 392, 394-396 and 402 are pending in the application.

Claims Rejections - 35 USC § 103

The claims stand rejected under 35 USC 103(a) as allegedly being unpatentable over **Mariotti** *et al.*, *Vaccine* 20:2229-2239 (2002) in view of WO 01/93804 to **Conley** *et al.*, and in view of **Joyce** *et al.*, *Carbohydrate Research*, 338:903-922 (2003). In summary, the Examiner states that Mariotti teaches the conjugation of peptides to CRM_{197}, that Conley teaches the capping of unreacted crosslinking agents on peptide-OMPC conjugates, and that Joyce teaches N-acetylcysteamine capping in the preparation of an immunogen.

In the response filed February 4, 2011, Applicants argued that even if a skilled artisan recognized that unreacted crosslinking agents on the carrier may undergo unwanted reactions, the immunogenicity results for the OMPC carrier exemplified in Conley (and Joyce) would not have provided the skilled artisan with a reasonable expectation that the carrier proteins recited in the presently claimed invention could be capped while preserving the functionality of the carriers such that they retain their ability to elicit the desired immune response against the peptide immunogen that would otherwise not occur without a carrier.

In the advisory action of March 8, 2011, the Examiner states that Applicants' argument that capped immunogenic conjugates may not retain immunogenicity does not place the application in condition for allowance because a skilled artisan would know to optimize the capping process by varying conditions and capping reagents, and then testing the resulting variants for retention of immunogenicity.

Applicants respectfully disagree. The presently claimed invention is not an optimization of a process discussed in the art. The prior art does not discuss capping in connection with any one of the claimed carrier proteins. Thus, it is not clear which conditions or capping reagents could be varied to arrive at the presently claimed invention. Nor would it have been obvious to try to cap any one of the claimed carrier proteins using a process discussed in connection with the OMPC carriers of Conley and Joyce because one of skill in the art could not have predicted whether the resulting conjugate would retain its ability to elicit the desired

immune response against the peptide immunogen that would otherwise not occur without a carrier, as presently claimed.

An Obvious to Try Rationale is Not Appropriate where the Results are Unpredictable

The Examination Guidelines Update for the application of the law of obviousness under 35 USC 103, published September 1, 2010 in the Federal Register (Vol. 75, No. 169, pp. 53643-60) indicates that an "Obvious to Try" rationale is only appropriate when (i) there is a recognized problem or need in the art, (ii) there are a finite number of identified predictable solutions to the recognized need or problem, and (iii) one of ordinary skill in the art could have pursued these known potential solutions with a reasonable expectation of success. *See* p. 53653, 2nd column.

Applicants reiterate that the use of capping reagents may disrupt the ability of the resulting conjugate to function as an immunogenic agent having the desired properties of the "carrier effect." *See* p. 6, 1st full paragraph of the Feb. 4, 2011 Response. As discussed in more detail below, not all carrier proteins are equivalent and the effect of capping on the immunogenicity of any particular carrier can not be predicted *ab initio*.

Although Conley and Joyce report that capped OMPC conjugates retain their immunogenicity, Applicants note that these results are in contrast to other results reported in the art. For example, Marburg *et al.* (US Pat. No. 5,623,057, cited in an IDS submitted August 20, 2008) reports that although capped pneumoccal polysaccharide-OMPC and MIEP (a purified subunit of OMPC) conjugates were capable of generating an immune response in mice (*see* Examples 12 and 22), this result is in contrast to pneumoccal polysaccharide-CRM and pneumoccal polysaccharide-DT (diphtheria toxin) conjugates, which *do not elicit measurable anti-pneumoccal polysaccharide antibody. See* column 43, lines 12-16. Similarly, Mond *et al.* (WO 93/15760, cited in an IDS submitted June 30, 2010) discusses a capped peptide (P74)-bovine serum albumin (BSA) conjugate (*see* paragraph bridging pp. 28-29 and the first full paragraph of p. 29), and reports that a good antibody response was elicited to the antigen *only* after the P74-BSA conjugate was further coupled to the large molecular weight T-independent antigen dextran. *See* p. 32, Example 3. Figure 6 (referred to in Example 3) shows that the P74-BSA conjugate was indistinguishable from P74 peptide alone and the uninjected control in

eliciting an anti-p74 peptide response in mice. Thus, one of skill in the art would not have had a reasonable expectation of success in the preparation of the conjugates of the presently claimed invention.

As discussed in the response of February 4, 2011, the presently claimed invention is based, in part, on Applicant's discovery that a capping molecule can be used with the claimed carrier proteins to avoid unwanted side reactions that may detrimentally impact the stability or safety of an immunogenic conjugate, while also preserving the conjugate's ability to elicit a desired immune response against the attached peptide immunogen. Immunogenic conjugates comprising a peptide immunogen coupled to each of the claimed carrier proteins, and capped as recited in the presently claimed invention are exemplified in the specification at Examples 1, 2 and 9. The immunogenicity of conjugates comprising each of the recited carriers is demonstrated in Examples 6 and 9, confirming that the functionality of the carrier proteins is preserved and the desired immune response is elicited.

In view of the foregoing, Applicants submit that the single exemplary carrier of Conley (and Joyce) would not have provided the skilled artisan with a reasonable expectation that the carrier proteins recited in independent claim 384 could be capped while preserving the functionality of the carrier to elicit the desired immune response against the peptide immunogen, as claimed. Accordingly, the presently claimed invention is patentable over the cited art.

Obviousness-Type Double Patenting Rejections

Claims 384, 386, 387, 392, 394-396 and 402 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claim 398 of copending Application No. 10/583,503.

Applicants reiterate that they will consider submitting a terminal disclaimer, if appropriate, to obviate this rejection upon an indication that the presently claimed invention is otherwise allowable.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-838-2045.

Respectfully submitted,

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